

### **EXAMINER'S AMENDMENT**

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Pamela Sherwood on July 15, 2010.

The application has been amended as follows:

A. Claims 1, 3, 6, 7 and 15 have been amended to read:

1. A method for detecting a predisposition to noncryptogenic liver disease in an individual human, the method comprising:

determining said predisposition to noncryptogenic liver disease by analyzing a biological sample from an individual human for a R340H alteration in keratin K8, wherein position 340 is relative to SEQ ID NO: 4, and wherein the presence of said alteration in keratin K8 is indicative of a predisposition to noncryptogenic liver disease in said individual human.

3. A method for detecting a predisposition to increased risk for viral hepatitis or acute fulminant hepatitis in an individual human, the method comprising:

determining said predisposition by analyzing nucleic acid of an individual human for a CGT to CAT nucleotide change at codon 340 of the keratin K8 gene, wherein the position of codon 340 is relative to SEQ ID NO: 4, and wherein the presence of CAT at

Art Unit: 1634

codon 340 of the keratin K8 gene is indicative of a predisposition to increased risk for viral hepatitis or acute fulminant hepatitis in said individual human.

6. The method of claim 3, wherein said analyzing the nucleic acid comprises the steps of:

amplifying a region of keratin K8 coding sequences from isolated genomic DNA or mRNA to provide an amplified fragment; and

detecting the presence of said nucleotide change in said amplified fragment.

7. The method of claim 6, wherein said detecting step comprises hybridization with a probe specific for said nucleotide change or digestion with specific restriction enzymes.

15. The method of claim 3, further comprising analyzing the individual human for one or more of the keratin K8 alterations selected from G52V, Y53H, G61C, G433S, and R453C.

B. Claim 16 has been added:

16. The method of claim 1, further comprising analyzing the individual human for one or more of the keratin K8 alterations selected from G52V, Y53H, G61C, G433S, and R453C.

C. The title has been amended to read:

--Keratin 8 Mutations are Risk Factors For Developing Liver Disease of Multiple Etiologies--

**The following is an examiner's statement of reasons for allowance:**

1. The previous rejection of the claims under 35 USC 112 first paragraph (enablement) is withdrawn in view of Applicant's arguments presented in the Appeal Brief of May 14, 2010 and in view of the clarification of the location of the keratin K8 "R341H" mutation referred to in the Declaration of August 28, 2009. In particular, the brief clarifies that, in the Declaration, the numbering of the amino acids in the keratin K8 protein is with respect to the mature protein which lacks the terminal methionine (see, e.g., page 10 of the brief). The previous rejection of claims 3, 6, and 7 under 35 USC 112 second paragraph has been obviated by the above amendment.

2. In the reply filed April 21, 2008 and May 29, 2008, Applicant elected Group 1 and the keratin K8 R340X mutation. In view of the allowability of claims 1, 3, 6 and 7, the previously withdrawn subject matter of methods which assay for the R340H mutation and which further assay for the mutations set forth in claims 15 and 16 are hereby rejoined and have been fully examined for patentability under 37 CFR 1.104.

Because these claims previously withdrawn from consideration have been rejoined, **the restriction requirement as set forth in the Office action mailed on March 19, 2008, as it pertained to methods which detect the elected R340X mutation and which detect this mutation in combination with the additional mutations recited in claims 15 and 16 is hereby withdrawn.** In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present

Art Unit: 1634

application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

3. The closest prior art of Ku et al (May 2001, November 2001, and March 2002) teach an association between the keratin K8 Y53H and G61C mutations and the occurrence of particular liver diseases. However, the cited Ku et al references do not teach the keratin K8 R340H mutation or an association between this mutation and predisposition to liver disease. Accordingly, the prior art does not teach or suggest the presently claimed methods for detecting a predisposition to noncryptogenic liver disease or predisposition to an increased risk for viral hepatitis or acute fulminant hepatitis comprising detecting in a biological sample of an individual human a R340H alteration in keratin K8, wherein position 340 is relative to SEQ ID NO: 4, and wherein the presence of said alteration in keratin K8 is indicative of a predisposition to noncryptogenic liver disease or an increased risk for viral hepatitis or acute fulminant hepatitis in said individual human.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Art Unit: 1634

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634